Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the AntiInfective Drugs Advisory Committee

January 30, 2001

Holiday Inn, The Ballrooms,
2 Montgomery Ave.,
Gaithersburg, MD. 20879

Members Present
L. Barth Reller, M.D.
Alan S. Cross, M.D.
Joan P. Chesney, M.D.
Celia Christie-Samuels, M.D.
David E. Soper, M.D.
Murray Wittner, M.D., Ph.D.
Gordon L. Archer, M.D.
Judith O'Fallon, M.D.
Barbara E. Murray, M.D.
James E. Leggett, Jr., M.D.
Ellen R. Wald, M.D.
Julio Ramirez, M.D.

FDA Participants
Diane Murphy, M.D.
Janice Soreth, M.D.
Mamodikoe Makhene, M.D.
He Sun, Ph.D.
Sousan Altaie, Ph.D.

Consultants
Steve Ebert, Pharm, D.
G. Scott Giebink, M.D.
Robert L. Danner, M.D.
Keith A.Rodvold, Pharm.D.

Guest Experts
Jose Vazquez, M.D.
Richard Besser, M.D.
Christopher Harrison, M.D.

These summary minutes for the January 30 meeting of the AntiInfective Drugs Advisory Committee were approved on February 28, 2001.

I certify that I attended the January 30 meeting of the AntiInfective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/S/_____
Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

_____/S/_____
L. Barth Reller, M.D.
Chair

This report contains public information that has not been reviewed by the agency or AntiInfective Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 12 days. External requests should be submitted to the Freedom of Information office.

The AntiInfective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 30, 2001 at the Holiday Inn, The Ballrooms, 2 Montgomery Ave., Gaithersburg, MD. 20879

The committee discussed new drug application (NDA) 50-755 for Augmentin ES™ (amoxicillin/clavulanate), 90 mg/kg/day, GlaxoSmithKline, for the treatment of pediatric patients with acute otitis media due to penicillin resistant *Streptococcus pneumoniae*.

The Committee had received a briefing document from the FDA and a background package from the Sponsor.

There were approximately 100 persons in the audience. The meeting was called to order at 8:00 a.m. by the Chair, L. Barth Reller, M.D. The Committee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the AntiInfective Drugs Advisory Committee read the Meeting Statement. Dianne Murphy, M.D., Director, Office of Drug Evaluation IV, provided the opening comments.

Janice Soreth, M.D., Acting Director, Division of Anti-Infective Drug Products began her presentation "AOM Trial Design" at 8:20. Scott Giebink, M.D., followed with "Overview of AOM due to penicillin resistant *S. pneumoniae*"

GlaxoSmithKline's presentation began at 9:00 and included the following topics and presenters:

Background/Overview	David Cocchetto, Ph.D.
PK/PD of Antibiotics in Otitis Media	William Craig, M.D.
Relevant Endpoint Analysis for Efficacy	Colin Marchant, M.D.
Augmentin ES Bacteriological & Clinical Efficacy in AOM	Brian Wynne, M.D.
Role of Augmentin ES in Treating AOM	George McCracken, M.D.

The Open Public Hearing portion of the meeting had no participants.

FDA's presentation began at 1:30 and included the following topics and presenters:

Augmentin ES for the treatment of Acute Otitis Media	Mamodikoe Makhene, M.D.
Augmentin Suspension – Summary of PK/PD Data	He Sun, Ph.D.
Breakpoint Presentation	Sousan Altaie, Ph.D.

The Committee began discussion of the questions and vote portion of the meeting at 3:30 with the following questions.

Questions for the Advisory Committee

1. To assess clinical response in an acute otitis media (AOM) trial targeting PRSP, what is the relevant test of cure?

   a- end of therapy (few days after last dose)
   b- later follow-up (1-3 weeks after last dose)

The Committee voted unanimously that "end of therapy" is the desired primary end point, and that in addition the "later follow-up" should be included as a secondary end point.
The vote 14

Would your answer be different in an AOM trial of "all comers" (no enrichment for PRSP)? Please explain.

No, more data is needed and the criteria should be the same regardless of the trial.

2. To assess microbiologic response in an AOM trial with a baseline tympanocentesis, what is the most informative repeat tap?

   a- on therapy
   b- end of therapy
   c- at time of clinical failure
   d- combination of above. Please specify.

The Committee was unanimous that it should be a "combination of the above".
*The vote 11 Members voted for **"a followed by c"** in order of importance.*
*3 Members voted for "**c followed by a"** in order of importance.*

3. In an AOM trial targeting PRSP, is a lower clinical cure rate for PRSP acceptable compared to cure rates in an "all comers" trial? Provide a lower bound of an acceptable clinical cure rate for patients with PRSP, taking into consideration the natural history of the disease.

This question was for the Committee to discuss and therefore the transcript will provide a record of the discussion in its entirety. The Committee did reflect a variety of points of view to this question ranging from acceptability if there were no other options, to no response available based on the information provided. In addition many conditions were discussed such as, the potential for finding acceptability of lower clinical cures leading to a slippery slope rather than looking for a natural fall off; the acceptance of a specified rate above the spontaneous resolution rate; the need to consider the time that the assessment is made; the confidence intervals; that it should be bug specific, and attributable to the drug, and effect of time on change in resistance.

4. Do the data support the safety and efficacy of Augmentin ES for the treatment of AOM due to PRSP?

   a- If yes, what would be the appropriate role for Augmentin ES in the treatment of AOM?
      - Empiric therapy?
      - Therapy for AOM due to documented PRSP?

   b- If no, what additional study (-ies) would you recommend?

The Committee was not able to answer the question as it was posed, because of the lack of upper boundaries. Instead it addressed itself to the following modified questions.

Do the data support the safety and efficacy of Augmentin ES for the treatment of AOM due to PRSP based on MIC of $\geq$2mcg to penicillin?

The vote 12 NO 2 YES

Do the data support the safety and efficacy of Augmentin ES for the treatment of AOM due to PRSP based on an amoxicillin MIC of $\leq$2mcg?

The votes 13 YES 1 Abstention

The Committee also indicated that studies are needed that provides better kinetics and higher numbers; that recommendation in labeling provide MIC boundaries;

5. Discuss the Sponsor's proposed breakpoint (4.0 mcg/ml) for Augmenting 14:1.

This question was for the Committee to discuss and therefore the transcript will provide a record of the discussion in its entirety.

The meeting was adjourned at 5:30 p.m.